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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,696	01/19/2001	Daniel S. Sem	P-TB 4567	6467

23601 7590 07/29/2003

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EXAMINER
BAKER, MAURIE GARCIA

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

file

Office Action Summary

Application No.	Applicant(s)
09/765,696	Sem
Examiner	**Art Unit**
Maurie G. Baker, Ph.D.	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 18, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *44-56* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *44-56* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *27*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The Response filed June 18, 2003 (Paper No. 26) is acknowledged. Claims 9, 11-14 and 37-43 were cancelled and claims 44-56 were added. Therefore, claims 44-56 are pending.

2. Newly added claims 44-56 read on the elected invention and species and thus are examined on the merits in this action.

Status of Rejections

3. The previous rejection under 35 USC 103 over He et al in view of Traxler et al is withdrawn in view of the claim amendments. However, the second rejection under 35 USC 103 (over He et al in view of Traxler et al and Rossman et al and Radzicka et al) is maintained over the newly filed claims (but has been slightly rewritten in light of the new claims). Applicant's arguments are addressed following the rejection. Also, new rejections necessitated by applicants' amendments are set forth below.

Maintained Rejections
Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Newly added claims 44-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over He et al (On PTO-1449; Bioorg. Med. Chem. Lett., 1994) in view of Traxler et al (On PTO-1449; J. Med. Chem., 1991) and Rossman et al (On PTO-1449; The Enzymes, 3rd Ed. 1975) and Radzicka et al (On PTO-1449; Methods Enzymol., 1995).

The following interpretations are used for this rejection: The specification defines a population as "a group of two or more different molecules" (page 14, line 4). He et al teach making two or more different molecules that comprise a common ligand (an ATP mimic; reading on the claimed "cofactor or mimic thereof") and a specificity ligand linked by a linker. The specificity ligand of He et al reads on the claimed "second ligand". As taught by the reference, these ligands can bind at least 2 different receptors from the same family (kinases) which bind ATP as a cofactor. The linker in the compounds of He et al is a simple methylene chain of variable length and as such would comprise a linker possessing perfect C2 symmetry as defined in the specification on page 10 (claims 13-14 and 42-43).

Specifically, He et al discuss the fact that kinases have two binding sites in the catalytic domain; one of these sites binds ATP while the other binds peptidic substrates (page 2845). He et al disclose making bisubstrate inhibitors "suitable to interact simultaneously with the ATP and the protein substrate binding domains" (page 2845, 2nd paragraph). The compounds contain an ATP mimic that would comprise the common ligand that is a "cofactor or mimic thereof". These compounds are of the general structure shown in Figure 2, with specific examples in Table 1. This ligand (ATP mimic) plus the methylene chain linker read on the claimed "module", with the different second

ligands of He reading on the "second ligand" of the instant claims. He et al teach second ligands that are either an amine or an amino acid. The second ligand creates differences in the binding of the compounds with two different kinases, protein kinase C (PKC) and c-AMP dependent protein kinase, as shown in Table 1. Changes in this second ligand are made due to differences in the binding sites of the two different kinases (page 2849), reading on different receptors in a receptor family of kinases.

He et al lack the specific teaching of identifying ligands that have *specificity for* a second receptor in the receptor family as the compounds of the reference only show specificity for PKC. However, it is noted that the "population" of compounds taught by He et al meets all of the limitations of a "population of bi-ligands" as described in the instant specification and that there are a wide variety of different kinases known in the art (see Traxler et al, for example, described below) that were not specifically tested by He et al. The properties of a compound are intrinsic to its structure and thus a "population" of compounds taught by He et al, having all of the required limitations, would also implicitly have the required binding characteristics. The instant claims contain ***no*** specific structural limitations whatsoever.

Furthermore, the synthesis of bisubstrate inhibitors for enzymes was extremely well established at the time of the invention. This is shown by the teachings of Traxler et al, for example. This reference also teaches bisubstrate inhibitors of kinases (see Abstract, Table I and section entitled "Concept and Design of Inhibitors"). The bisubstrate inhibitors of Traxler et al ***do*** show specificity for more than one enzyme in the kinase family, see Table II. The reference also teaches that a variety of kinases have

known and distinct substrate specificities and that with this knowledge, "design of selective inhibitors of this class of enzymes should be possible" (page 2328). Traxler et al also teach that "bisubstrate inhibitors ...have the potential for high selectivity and potency" (page 2328, 2nd column).

With respect to the species of dehydrogenase and nicotinamide adenine dinucleotide (or nicotinamide adenine dinucleotide phosphate), the following is noted. Rossman et al teach that dehydrogenases bind nicotinamide adenine dinucleotide as a cofactor and that that a variety of structures of dehydrogenase enzymes are known (see, for example, page 64 and page 70). The reference also teaches that there is structural similarity between dehydrogenases and kinases (see section 2, pages 96-98). Also, Radzicka et al teach that "transition state and multisubstrate inhibitors have been prepared against enzymes catalyzing reactions of every class" (page 288) and that such molecules "may express a large entropic advantage in binding" (page 287).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to perform the method of He et al to identify ligands that have specificity for a second receptor in the receptor family, when the family is dehydrogenases binding nicotinamide adenine dinucleotide (or nicotinamide adenine dinucleotide phosphate), in view of the teachings of Traxler et al, Rossman et al and Radzicka et al. The general conditions of identifying bisubstrate inhibitors "suitable to interact simultaneously" two sites of an enzyme was well-known as taught by He et al and also Radzicka et al. Radzicka et al teach that "transition state and multisubstrate inhibitors have been prepared against enzymes catalyzing reactions of every class". One

of ordinary skill would have been motivated to create different bisubstrate inhibitors because the similarity between the structures and properties is sufficiently close that one of ordinary skill would have been motivated to make additional inhibitors in searching for more potent compounds. As taught by Traxler et al, once the substrate specificity of an enzyme is known, it is obvious to design new bisubstrate inhibitors based on this knowledge and "bisubstrate inhibitors ...have the potential for high selectivity and potency". Moreover, Rossman et al teach that there is structural similarity between dehydrogenases and kinases, thus the application of the method of He et al to the dehydrogenase family would be obvious to one of ordinary skill.

Response to Arguments

6. Applicant's arguments filed June 18, 2003 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

7. Applicant argues that the references do not teach the claimed invention and that there is no motivation to combine the references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Also, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what

the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The examiner maintains that the combined teachings of the cited references denote the level of ordinary skill and would have suggested the claimed invention to one of ordinary skill thus rendering the claimed invention *prima facie* obvious for the reasons set forth in the rejection.

8. Note that the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the instant case, the beneficial result of the combination of references is creating a population of compounds from which to assay for more active members, since (as taught by Traxler et al), "bisubstrate inhibitors ...have the potential for high selectivity and potency".

9. Applicants argue that the cofactors for kinases and dehydrogenases have different structures and that all kinases and dehydrogenases do not share structural similarity (Response, page 10). Applicants also state that the enzymes would "have completely different positions proximal to a specificity site that would allow a linker to be placed so that the common ligand and a second ligand are oriented to bind their respective binding sites" and have different reaction mechanisms. While this may be true, it is unclear how this is material to the instant claims. It is noted that the features upon which applicant relies (i.e., specific structures and/or

linking sites) are not recited in the rejected claim(s). That is, the claims do not show the linkage points and/or linker for the population of bi-ligands. In fact, the claims show **no** specific structures whatsoever. Please also see paragraphs 10, 12 and 14 below.

10. Applicant's newly filed claims are directed to a "method for identifying a population of bi-ligands" specifically either (1) to dehydrogenases {claim 44}; (2) to enzymes that bind nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate as a cofactor {claim 47}; or (3) both {claim 52}. Applicants argue that the references are not applicable since there is no specific structural similarity between kinases and dehydrogenases and make other arguments based on specific structural requirements. Again, the claims show **no** specific structure and, importantly, do not show what structure is critical for the claimed activity (see 35 U.S.C. 112 rejections below). The art clearly teaches the general concept of linking ligands together to create bisubstrate inhibitors for enzymes and motivation to do so for dehydrogenases. Thus, the examiner does not find the arguments based on specific structure to be persuasive and maintains that the claimed invention would have been *prima facie* obvious to one of ordinary skill.

New Rejections
Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Newly added claims 44-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Applicant's newly filed claims are directed to a "method for identifying a population of bi-ligands" specifically either (1) to dehydrogenases {claim 44}; (2) to enzymes that bind nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate as a cofactor {claim 47}; or (3) both {claim 52}.

The specification discloses **no** examples of the preparation and use of such "population of bi-ligands". Most importantly, with respect to the newly filed claims, the populations of bi-ligands that satisfy the conditions (1), (2) and/or (3) above, essential to applicant's invention, are not adequately described in the instant disclosure. The language of the specification should describe the claimed invention so that one skilled in the art can recognize what is claimed. A description of a compound in terms of its function fails to distinguish the compound from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. It is recognized that the claimed

invention is a method; however, the product made by the claimed method is simply not described.

Note that adequate disclosure, like enablement, requires representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that applicant had possession of the full scope of the claimed invention. The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

A representative number of species means that the species that are adequately described are representative of the entire genus. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Therefore it is deemed that the instant specification lacks adequate support *specifically* relating to the newly claimed genus of populations of bi-ligands that satisfy the conditions (1), (2) and/or (3) above. The instant specification is neither representative of the claimed genus, nor does it represent a substantial portion of the claimed genus. Moreover, the claimed genus encompasses members which are yet to be prepared or envisioned in the context of the newly claimed invention. This further evidences that instant disclosure does not constitute support for the claimed genus or a substantial portion thereof.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Newly added claims 44-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the structures of the compounds, e.g. the linker structure and linkage sites, that brings about the claimed binding activity *specific to* (1) dehydrogenases {claim 44}; (2) enzymes that bind nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate as a cofactor {claim 47}; or (3) both {claim 52}.

Status of Claims/ Conclusion

15. No claims are allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner is on an increased flextime schedule but can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

18. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie Garcia Baker, Ph.D.
July 24, 2003